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Prediction and prevention of radiation-induced swallowing dysfunction

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CHAPTER 3

Predictive modelling for swallowing dysfunction after primary (chemo)radiation: results of a prospective observational study

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Abstract

Background and purpose: The purpose of this large multicenter prospective cohort study was to identify which dose-volume histogram parameters and pre-treatment factors are most important to predict physician-rated and patient-rated radiation-induced swallowing dysfunction (RISD) in order to develop predictive models for RISD after curative (chemo) radiotherapy ((CH) RT).

Material and methods: The study population consisted of 354 consecutive head and neck cancer patients treated with (CH) RT. The primary endpoint was grade 2 or more swallowing dysfunction according to the RTOG/EORTC late radiation morbidity scoring criteria at 6 months after (CH) RT. The secondary endpoints were patient-rated swallowing complaints as assessed with the EORTC QLQ-H&N35 questionnaire. To select the most predictive variables a multivariate logistic regression analysis with bootstrapping was used.

Results: At 6 months after (CH) RT the bootstrapping procedure revealed that a model based on the mean dose to the superior pharyngeal constrictor muscle (PCM) and mean dose to the supraglottic larynx was most predictive.

For the secondary endpoints different predictive models were found: for problems with swallowing liquids the most predictive factors were the mean dose to the supraglottic larynx and radiation technique (3D-CRT versus IMRT). For problems with swallowing soft food the mean dose to the middle PCM, age (18-65 versus > 65 years), tumor site (nasopharynx vs other sites) and radiation technique (3D-CRT versus IMRT) were the most predictive factors. For problems with swallowing solid food the most predictive factors were the mean dose to the superior PCM, the mean dose to the supraglottic larynx and age (18-65 versus > 65 years). And for choking when swallowing the V60 of the esophageal inlet muscle and the mean dose to the supraglottic larynx were the most predictive factors.

Conclusions: Physician-rated and patient-rated RISD in head and neck cancer patients treated with (CH) RT cannot be predicted with univariate relationships between the dose distribution in a single organ at risk and an endpoint. Separate predictive models are needed for different endpoints, and factors other than dose-volume histogram parameters are important as well.

Introduction

Swallowing dysfunction after curative (chemo) radiotherapy ((CH) RT) in head and neck cancer (HNC) has a significant impact on health-related quality of life (HRQoL)¹⁻⁷. As the incidence of radiation-induced xerostomia is reduced by the use of new radiation techniques, such as intensity-modulated radiotherapy (IMRT)⁸, the problem of swallowing dysfunction is becoming one of the most relevant side effects of (CH) RT.

Radiation-induced swallowing dysfunction (RISD) has been associated with a variety of motility disorders, which most likely result from mucosal swelling and fibrosis of the multiple muscles and other structures involved in swallowing^{1,9-12}. Indeed, a number of authors found significant relationships between the dose distributions in swallowing organs at risk (SWOARs) and RISD, such as the dose to the pharyngeal constrictor muscles (PCMs) and glottic and supraglottic regions¹³⁻¹⁸. However, most of these studies only investigated univariate relationships between the dose distributions to potential SWOARs and different aspects of RISD and did not take into account other potential confounding and/or independent prognostic factors, such as the addition of concomitant chemotherapy to radiation, fractionation schedules and the primary tumor site¹⁹⁻²². Data published so far do not provide sufficient information regarding which Dose-Volume Histogram (DVH) parameters of the SWOARs are most important in predicting RISD and how they can be used for treatment planning optimization. To be able to test the value of adequate numbers of potential prognostic factors, large prospective cohort studies and sophisticated statistical methods are required for the development of reliable predictive models.

Therefore, the purpose of this large prospective cohort study was to identify the most important DVH-parameters and other pre-treatment factors that determine physician-rated and patient-rated RISD in order to develop predictive models for RISD after curative (CH) RT.

Methods and Materials

Patients

The study population of this prospective cohort study consisted of 354 consecutive patients, treated from 1997 either in the VU University Medical Center (VUMC), Amsterdam or in the University Medical Center Groningen (UMCG), Groningen, the Netherlands. Table 1 shows the demographic, tumor and treatment characteristics of the study population. All patients were treated with curatively intended conventional three-dimensional conformal RT (3D-CRT) or intensity-modulated RT (IMRT) for HNC, either alone or in combination with concomitant chemotherapy or cetuximab. All patients were subjected to a standardized follow-up program which included prospective evaluation of toxicity and HRQoL, prior to, during and at regular intervals after curative (CH) RT. Acute and late toxicity were graded according to the RTOG/EORTC Radiation Morbidity Scoring Criteria²³.

HRQoL was assessed using the EORTC QLQ-C30 and the additional head and neck cancer module (the EORTC QLQ-H&N35)^{24–26}.

Patients who previously underwent surgery, radiotherapy and/or chemotherapy, who had prior malignancies, and/or distant metastases were excluded. Patients with RTOG grade 2–4 swallowing dysfunction at baseline were also excluded in order to ensure that the observed swallowing dysfunction was induced by radiation treatment itself and not by tumor extension. Patients with recurrences at 6 months were also excluded.

Table 1: Patients characteristics

Characteristics		Number	%
Sex	Male	261	74
	Female	93	26
Age, years	18–65	222	63
	> 65	132	37
Tumor classification *	T0	16	5
	T1	64	18
	T2	151	43
	T3	68	19
	T4	55	15
Node classification *	N0	200	57
	N1	39	11
	N2a	15	4
	N2b	38	11
	N2c	53	15
Primary Site	N3	9	2
	Larynx	164	47
	Oropharynx	91	26
	Oral cavity	19	5
	Hypopharynx	18	5
	Nasopharynx	14	4
	Unknown primary	8	3
Treatment modalities	Other	40	11
	Conventional radiotherapy	95	27
	Accelerated radiotherapy	188	53
Radiation technique	Chemoradiation	71	20
	3D-CRT	219	62
	IMRT	135	38
Baseline swallowing dysfunction (RTOG)	Grade 0	304	86
	Grade 1	50	14

* According to the UICC TNM-classification, 7th edition, 2009. Abbreviations: 3D-CRT=3D conformal radiotherapy, IMRT=intensity modulated radiotherapy, RTOG=Radiation Therapy Oncology Group

Endpoints

The primary endpoint was defined as grade 2–4 swallowing dysfunction according to the RTOG/EORTC Late Radiation Morbidity Scoring Criteria as assessed 6 months after completion of (CH) RT (SWALM6). This time point was chosen as swallowing dysfunction at 6

months after treatment turned out to be very predictive for swallowing dysfunction at subsequent time points²⁰.

The secondary endpoints were moderate to severe patient-rated swallowing complaints at 6 months after (CH) RT as assessed with the EORTC QLQ-H&N35 questionnaire. For these endpoints, 4 questions related to swallowing were used, including questions 35 ("Have you had problems swallowing liquids?"), 36 ("Have you had problems swallowing soft food?"), 37 ("Have you had problems swallowing solid food?") and 38 ("Have you choked when swallowing?").

Treatment

Until the end of 2007, the majority of patients were treated with 3D-CRT. Since 2008 patients were increasingly treated with IMRT. Radiotherapy was delivered using megavoltage equipment (6 MV linear accelerator). For all patients, a contrast-enhanced planning CT-scan was made in supine treatment position.

Patients with early glottic carcinoma were treated with a fraction dose of 2 Gy (5 or 6 times/week) up to a total dose of 66 Gy. These patients were irradiated at the primary site without elective neck treatment. Patients treated with concomitant CHRT were irradiated with a conventional fractionation schedule (2 Gy per fraction, 5 times per week up to 70 Gy in 7 weeks). In case of primary radiotherapy of the more advanced tumors, which were considered ineligible for CHRT, an accelerated schedule with concomitant boost technique was used, either or not combined with cetuximab. These patients were treated with 6 fractions per week with a second fraction on Friday afternoon with a minimum interval of 6 hours, up to a total dose of 70 Gy in 6 weeks.

In patients treated with 3D-CRT, no attempts were made to spare the salivary glands. Most of these patients received bilateral elective irradiation of the neck nodes to a total dose of 46 Gy and a boost on the primary tumor and pathological lymph nodes to a total dose of 70 Gy.

IMRT treatments attempted to spare the parotid glands without compromising the dose to the target volumes. In general, 7-field equidistant, non-opposing beams were applied. All IMRT treatments applied a simultaneous integrated boost (SIB). Most patients received bilateral elective irradiation of the neck nodes to a total dose of 54.25 Gy, in fractions of 1.55 Gy. The primary tumor and pathological lymph nodes were treated to a total dose of 70 Gy, in 2 Gy fractions.

Chemotherapy was given concurrently with conventionally fractionated radiotherapy and consisted of cisplatin 100 mg/m² on days 1, 22 and 43 (in the VUMC), or carboplatin on day 1 (300-350 mg/m² in 30 minutes intravenously) and 5-fluorouracil (5-FU) from day 1 to 4 by continuous infusion (600 mg/m²/24 hours), consisting of 3 courses given with an interval of 3 weeks (in the UCMG).

Contouring of organs at risk

The SWOARs were delineated by one radiation oncologist, according to the guidelines for SWOARs potentially involved in RISD as described by Christianen et al.²⁷ including the superior, middle and inferior PCM, the cricopharyngeal muscle, the esophagus inlet muscle (EIM), the cervical esophagus, the base of tongue and the supraglottic and glottic larynx. The parotid and submandibular salivary glands were delineated according to the guidelines described by Van de Water et al.²⁸.

Dose distribution calculations

Since different treatment planning systems were used in the VUMC and the UMCG, all data (i.e., contours and dose distributions) were transferred to the VODCA software program (VODCA Company: viewer version 4.2.2. and database version 4.1.1). This system allows reconstruction of the original dose distributions in all aforementioned potential OARs and the generation of DVHs. Finally, all DVH data (the mean dose and the V5 up and until the V70) were merged with all other potential pre-treatment prognostic factors for each individual patient into one database.

Statistics

For the development of the predictive models for all endpoints, a multivariate logistic regression analysis was used with an extended bootstrapping technique and forward variable selection as described by El Naqa et al.²⁹. In contrast to the methods described by El Naqa et al.²⁹, we used the likelihood criterion, instead of correlation measures. The average likelihood was calculated over all test data sets for each combination of variables. The model which gave the highest average likelihood was selected as the most predictive model.

Based on a former analysis by Langendijk et al.²⁰, we divided the variable *primary tumor site* into 2 groups, including oropharynx and nasopharynx versus all other sites.

Before carrying out the regression analysis, a correlation matrix was produced to check for high correlations between potential prognostic factors, in particular between DVH-parameters. In case of Pearson correlation coefficients ≥ 0.80 between candidate prognostic factors, only one variable was selected and entered in the model in order to avoid the problem of multicollinearity which may negatively affect the generalizability of the model.

The multivariate logistic regression was performed with 2000 bootstraps for each analysis. For every model order, and every prognostic factor, the average total likelihood of the predictions was calculated. The set of factors with the highest average total likelihood was selected for the definite predictive models for SWALM6 and patient-rated swallowing dysfunction.

Adjusted Odds ratios (OR) and 95% confidence intervals (95% CI) were calculated for the selected variables in the models. For each patient, predictions (i.e., NTCP values) were

calculated using the set of n prognostic variables (x), and the regression coefficients (θ) according to the formula:

$NTCP = (1 + e^{-S})^{-1}$, in which

$$S = \beta_0 + \sum_{i=1}^n \beta_i \cdot x_i$$

Calculation of the NTCP values is also presented in nomograms (see Appendices). The NTCP curves for the different categories are depicted in figures.

Model performance was determined by calculating the area under the curve (AUC) of the Receiver Operating Characteristics.

Results

Variable reduction and dose distribution procedure

A very strong correlation was found between almost all DVH parameters within each swallowing organ at risk (SWOAR) and the mean dose of that SWOAR. Therefore, we include only the mean doses of all SWOARs in the analysis, except for the esophagus inlet muscle (EIM). For that structure the correlation between the mean dose and the V50 and the V60 was low, and therefore we entered the mean dose as well as the V50 and V60 in the analyses. In addition, the correlation between the mean dose in the ipsilateral and contralateral parotid, and submandibular glands, was very strong. Therefore, we used the mean dose in the ipsi- and contralateral parotid gland as one single variable. The same procedure was followed for the submandibular glands.

Primary endpoint: physician-rated swallowing dysfunction 6 months after (CH) RT (SWALM6)

In the univariate analysis, the mean dose to the superior pharyngeal constrictor muscle (PCM), the middle PCM, the EIM, the cervical esophagus, the base of tongue, the supraglottic larynx, the parotid glands, and the submandibular glands, as well as the V50 of the EIM were significantly associated with SWALM6 (Table 2). In addition, T-stage (T1-2 versus T3-4), N-stage (N0 versus N+), tumor site (oropharynx/nasopharynx versus other sites), concomitant chemotherapy, bilateral neck irradiation and baseline swallowing dysfunction (grade 0 versus grade 1) were also significant associated with SWALM6.

The variables included as candidate prognostic factors in the multivariate model are similar to those listed in Table 2. In the multivariate logistic regression analysis, the average likelihood of bootstrap prediction was optimal with a model consisting of two variables, including the mean dose to the superior PCM and the mean dose to the supraglottic larynx. Model performance was good with an AUC of 0.80 (95% CI 0.75 – 0.85). The OR's

Table 2: Results of the univariate analysis of the primary and secondary endpoints

Variable	Endpoints at 6 months after completion of radiotherapy									
	Endpoints at 6 months after completion of radiotherapy		Q35: Problems swallow- Q36: Problems swallow- Q37: Problems swallow- Q38: Choking when		Q35: Problems swallow- Q36: Problems swallow- Q37: Problems swallow- Q38: Choking when		Q35: Problems swallow- Q36: Problems swallow- Q37: Problems swallow- Q38: Choking when		Q35: Problems swallow- Q36: Problems swallow- Q37: Problems swallow- Q38: Choking when	
	lowing dysfunction	ing liquids	ing soft food	ing solid foods	swallowing	lowing dysfunction	ing liquids	ing soft food	ing solid foods	swallowing
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)
Mean dose superior PCM (Gy)	1.06 (1.04-1.08) < .01	1.02	1.04 (1.00-1.04)	.027	1.04 (1.02-1.06) < .01	1.05 (1.03-1.07) < .01	1.05 (1.03-1.07) < .01	1.00 (0.98-1.02) ns		
Mean dose middle PCM (Gy)	1.06 (1.04-1.09) < .01	1.05	1.02 (1.02-1.07) < .01	1.06 (1.03-1.09) < .01	1.06 (1.03-1.09) < .01	1.06 (1.03-1.09) < .01	1.02 (0.99-1.05) ns			
Mean dose inferior PCM (Gy)	1.01 (0.99-1.03) ns	1.04	1.01 (1.01-1.07) .013	1.02 (0.99-1.04) ns	1.02 (1.00-1.05) .047	1.02 (1.00-1.05) .047	1.07 (1.01-1.13) .016			
Mean dose cricopharyngeal muscle (Gy)	1.01 (0.99-1.02) ns	1.03	1.00 (1.00-1.05) .026	1.00 (0.99-1.02) ns	1.02 (0.99-1.04) ns	1.02 (0.99-1.04) ns	1.04 (1.00-1.07) .033			
Mean dose EIM (Gy)	1.03 (1.01-1.04) < .01	1.01	0.99 (0.99-1.03) ns	1.01 (0.99-1.03) ns	1.03 (1.01-1.05) < .01	1.02 (0.99-1.05) ns				
V50 EIM (%)	1.01 (1.00-1.02) < .01	1.00	0.99 (0.99-1.01) ns	1.00 (0.99-1.01) ns	1.01 (1.00-1.02) ns	1.02 (1.01-1.03) < .01				
V60 EIM (%)	1.01 (0.99-1.02) ns	1.01	0.99 (0.99-1.02) ns	1.00 (0.99-1.02) ns	1.01 (1.00-1.02) .048	1.03 (1.01-1.04) < .01				
Mean dose cervical esophagus (Gy)	1.04 (1.02-1.05) < .01	1.01	0.99 (0.99-1.03) ns	1.02 (1.00-1.04) .003	1.03 (1.01-1.05) < .01	1.02 (0.99-1.05) ns				
Mean dose base of tongue (Gy)	1.06 (1.04-1.08) < .01	1.02	0.99 (0.99-1.03) ns	1.04 (1.02-1.06) < .01	1.04 (1.02-1.07) < .01	1.00 (0.98-1.02) ns				
Mean dose supraglottic larynx (Gy)	1.05 (1.02-1.07) < .01	1.08	1.04 (1.04-1.13) < .01	1.05 (1.02-1.08) < .01	1.05 (1.02-1.09) < .01	1.09 (1.02-1.16) < .01				
Mean dose glottic larynx (Gy)	1.01 (0.99-1.02) ns	1.02	1.00 (1.00-1.05) .045	1.01 (0.99-1.03) ns	1.01 (0.99-1.03) ns	1.04 (1.00-1.08) .04				
Mean dose parotid glands (Gy)	1.05 (1.04-1.07) < .01	1.02	1.00 (1.00-1.04) .027	1.03 (1.02-1.05) < .01	1.05 (1.03-1.07) < .01	1.02 (0.99-1.04) ns				
Mean dose submandibular glands (Gy)	1.05 (1.03-1.07) < .01	1.03	1.01 (1.01-1.05) < .01	1.04 (1.02-1.06) < .01	1.05 (1.03-1.07) < .01	1.01 (0.99-1.03) ns				
Sex (male vs. female)	0.86 (0.50-1.46) ns	1.26	0.59 (0.59-2.71) ns	1.08 (0.50-2.35) ns	0.47 (0.19-1.19) ns	0.52 (0.15-1.81) ns				
Age (18-65 vs. >65 years)	0.68 (0.41-1.13) ns	1.30	0.65 (0.65-2.59) ns	1.68 (0.86-3.29) ns	1.03 (0.54-1.98) ns	2.14 (0.86-5.33) ns				
T-stage (T0-2 vs. T3-4)	2.98 (1.82-4.87) < .01	0.68	0.30 (0.30-1.57) ns	1.14 (0.56-2.35) ns	1.36 (0.67-2.75) ns	1.14 (0.44-2.94) ns				
N-stage (N0 vs. N+)	4.56 (2.72-7.64) < .01	0.88	0.43 (0.43-1.82) ns	2.25 (1.14-4.44) .019	2.38 (1.23-4.60) .01	0.45 (0.16-1.27) ns				
Tumor site (others vs. oro-/nasopharynx)	4.61 (2.77-7.67) < .01	1.43	0.67 (0.67-3.02) ns	2.92 (1.46-5.86) < .01	3.19 (1.57-6.49) < .01	0.63 (0.21-1.95) ns				
Concomitant chemotherapy (no vs. yes)	3.94 (2.28-6.83) < .01	1.42	0.60 (0.60-3.35) ns	2.79 (1.29-6.06) < .01	2.20 (0.96-5.00) ns	0.22 (0.03-1.65) ns				
Radiation technique (3D-CRT vs. IMRT)	1.57 (0.97-2.54) ns	0.31	0.12 (0.12-0.76) .011	0.60 (0.28-1.29) ns	0.86 (0.43-1.76) ns	0.30 (0.09-1.03) ns				
Accelerated radiotherapy (no vs. yes)	0.79 (0.49-1.27) ns	1.11	0.55 (0.55-2.27) ns	0.70 (0.36-1.38) ns	1.01 (0.52-1.97) ns	0.97 (0.38-2.44) ns				
Bilateral neck irradiation (no vs. yes)	5.96 (2.87-12.3) < .01	3.46	1.39 (1.39-8.63) < .01	3.38 (1.36-8.37) < .01	5.11 (2.07-12.61) < .01	1.96 (0.64-6.02) ns				
Baseline swallowing dysfunction (RTOG grade 0 vs. 1)	3.27 (1.76-6.06) < .01	not applicable	not applicable	not applicable	not applicable	not applicable				
Swallowing complaints (no vs. mild)	not applicable	0.77 (0.33-1.77) ns	1.61 (0.73-3.55) ns	2.45 (1.24-4.82) < .01	4.22 (1.62-10.99) < .01					

Abbreviations: 3D-CRT= 3D conformal radiotherapy, CI=confidence interval, EIM=esophagus inlet muscle, IMRT= intensity modulated radiotherapy, ns= not significant, OR= odds ratio, p= p-value, PCM=pharyngeal constrictor muscle, RTOG= Radiation Therapy Oncology Group, Vx=volume receiving zx Gy

for each of the 2 selected variables are shown in Table 3. The NTCP value for the individual patient can be calculated using the formula:

$NTCP = (1 + e^{-S})^{-1}$, in which

$S = -6.09 + (\text{mean dose PCM superior} \times 0.057) + (\text{mean dose supraglottic larynx} \times 0.037)$.

The NTCP curves for the different categories are depicted in Figure 1. Alternatively the NTCP value for each individual patient can be determined using the nomogram for SWALM6 as depicted in appendix A.

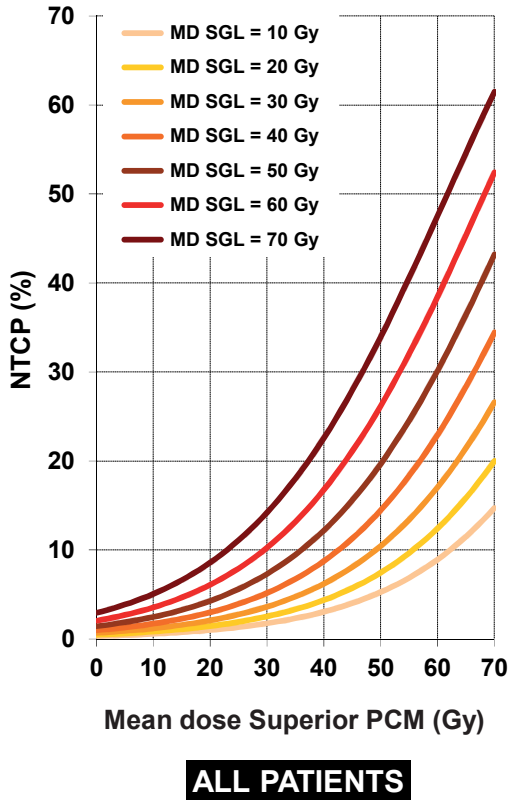


Figure 1. Normal tissue complication probability curves for SWALM6 for each 10 Gy increase in dose to the supraglottic larynx. Abbreviations: MD SGL=mean dose supraglottic larynx, NTCP=normal tissue complication probability, PCM=pharyngeal constrictor muscle.

Secondary endpoints: patient rated swallowing dysfunction

The results of the univariate logistic regression analysis for the four patient-rated endpoints are listed in Table 2.

Problems with swallowing liquids

For problems with swallowing liquids, the model was most optimal with two variables, including the mean dose to the supraglottic larynx and radiation technique (3D-CRT versus IMRT). The AUC for this 2-factor model was 0.75 (95% CI 0.68 – 0.83). The OR's for each of the 2 selected variables are shown in Table 3. The NTCP value for the individual patient can be calculated using the formula:

$NTCP = (1 + e^{-S})^{-1}$, in which

$S = -5.98 + (\text{mean dose supraglottic larynx} \times 0.074) + (\text{radiation technique} \times -1.209)$.

The NTCP curves for the different categories are depicted in Figure 2a, and the nomogram for problems with swallowing liquids in appendix B1.

Problems with swallowing soft food

For problems with swallowing soft food, the model was most optimal with four variables, including the mean dose to the middle PCM, age (18-65 versus > 65 years), tumor site (oropharynx/nasopharynx versus other sites), and radiation technique (3D-CRT versus IMRT). The AUC for this 4-factor model was 0.79 (95% CI 0.72 – 0.86). The OR's for each of the 4 selected variables are shown in Table 3. The NTCP value for the individual patient can be calculated using the formula:

$NTCP = (1 + e^{-S})^{-1}$, in which

$S = -5.83 + (\text{mean dose middle PCM} \times 0.061) + (\text{age} \times 1.203) + (\text{tumor site} \times 1.122) + (\text{radiation technique} \times -0.912)$.

The NTCP curves for the different categories are depicted in Figure 2b, and the nomogram for problems with swallowing soft food can be found in appendix B2.

Problems with swallowing solid food

For problems with swallowing solid food, the model was most optimal when consisting of three variables, including the mean dose to the superior PCM, the mean dose to the supraglottic larynx, and age (18-65 versus > 65 years). The AUC for this 3-factor model was 0.78 (95% CI 0.71 – 0.85). The OR's for each of the 3 selected variables are shown in Table 3. The NTCP value for the individual patient can be calculated using the formula:

$NTCP = (1 + e^{-S})^{-1}$, in which

$S = -6.89 + (\text{mean dose superior PCM} \times 0.049) + (\text{mean dose supraglottic larynx} \times 0.048) + (\text{age} \times 0.795)$.

The NTCP curves for the different categories are depicted in Figure 2c, and the nomogram for problems with swallowing solid food in appendix B3.

Choking when swallowing

For choking when swallowing, the model was most optimal with two variables, including the V60 of the EIM and the mean dose to the supraglottic larynx. The AUC for this 2-factor model was 0.77 (95% CI 0.67 – 0.86). The OR's for each of the 2 selected variables are shown in Table 3. The NTCP value for the individual patient can be calculated using the formula:

$NTCP = (1 + e^{-S})^{-1}$, in which

$S = -7.07 + (V60 \text{ EIM} \times 0.020) + (\text{mean dose supraglottic larynx} \times 0.066)$.

The NTCP curves for the different categories for choking when swallowing are depicted in Figure 2d, and the nomogram in appendix B4.

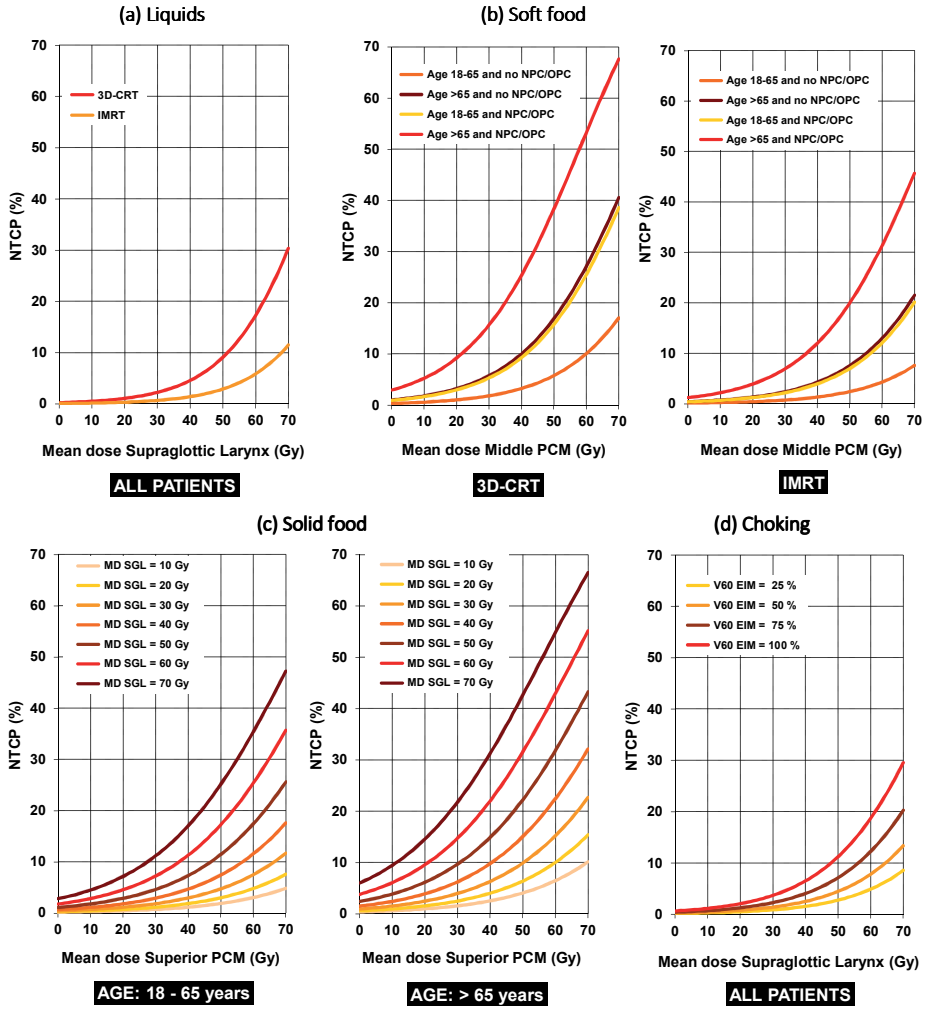


Figure 2. Normal tissue complication probability curves for patient rated swallowing dysfunction: (a) Liquids, (b) Soft food, (c) Solid food, (d) Choking. Abbreviations: 3D-CRT=3D conformal radiotherapy, EIM=esophagus inlet muscle, IMRT=intensity modulated radiotherapy, MD SGL=mean dose supraglottic larynx, NPC=nasopharyngeal cancer, NTCP=normal tissue complication probability, OPC=oropharyngeal cancer, PCM=pharyngeal constrictor muscle, V60=volume receiving ≥ 60 Gy.

Table 3: Results of the multivariate analysis for the primary and secondary endpoints

Variable	β	OR	95% CI	p-value	AUC	95% CI
Model for Grade 2-4 RTOG late swallowing dysfunction					0.80	0.75 - 0.85
Mean dose superior PCM (Gy)	0.057	1.06	1.04 - 1.08	< .01		
Mean dose supraglottic larynx (Gy)	0.037	1.04	1.01 - 1.06	< .01		
Model for Q35: Problems with swallowing liquids (moderate to severe)					0.75	0.68 - 0.83
Mean dose supraglottic larynx (Gy)	0.074	1.08	1.03 - 1.12	< .01		
Radiation technique (3D-CRT vs. IMRT)	-1.209	0.30	0.12 - 0.76	.011		
Model for Q36: Problems with swallowing soft food (moderate to severe)					0.79	0.72 - 0.86
Mean dose middle PCM (Gy)	0.061	1.06	1.03 - 1.10	< .01		
Age (18-65 vs. > 65 years)	1.203	3.33	1.50 - 7.41	< .01		
Tumor site (Other sites vs. oro-/nasopharynx)	1.122	3.07	1.37 - 6.90	< .01		
Radiation technique (3D-CRT vs. IMRT)	-0.912	0.40	0.17 - 0.93	.032		
Model for Q37: Problems with swallowing solid food (moderate to severe)					0.77	0.70 - 0.84
Mean dose superior PCM (Gy)	0.049	1.05	1.03 - 1.07	< .01		
Mean dose supraglottic larynx (Gy)	0.048	1.05	1.01 - 1.09	< .01		
Age (18-65 vs. > 65 years)	0.795	2.21	1.02 - 4.79	.044		
Model for Q38: Choking when swallowing (moderate to severe)					0.77	0.67 - 0.86
V60 esophageal inlet muscle (%)	0.020	1.02	1.01 - 1.03	< .01		
Mean dose supraglottic larynx (Gy)	0.066	1.07	1.00 - 1.36	.042		

Abbreviations: 3D-CRT=3D conformal radiotherapy, AUC=area under the curve of the curve, CI=confidence interval, IMRT=intensity modulated radiotherapy, OR=odds ratio, PCM=pharyngeal constrictor muscle, RTOG= Radiation Therapy Oncology Group, V60=volume receiving ≥ 60 Gy.

Discussion

The primary objective of the current study was to develop a predictive model for grade 2-4 swallowing dysfunction according to the RTOG/EORTC Late Radiation Morbidity Scoring Criteria as assessed 6 months after completion of (CH) RT (SWALM6). The analysis showed that the combination of two factors, including the mean dose to the superior pharyngeal constrictor muscle and the mean dose to the supraglottic larynx provided a predictive model with good performance.

To our knowledge, this is the first prospectively designed cohort study that specifically aimed at developing a predictive model for radiation induced swallowing dysfunction (RISD) in HNC patients treated with primary curatively intended (CH) RT. The prospective design of this study had several advantages. First, by assessing swallowing dysfunction at baseline, we could exclude patients who already had grade 2-4 swallowing dysfunction prior to (CH) RT. As we were primarily interested in *radiation-induced* swallowing dysfunction, we decided to exclude these patients as their swallowing dysfunction was most likely caused by local tumor extension. As a consequence, the predictive model presented in this paper is only applicable for those patients without grade 2-4 swallowing dysfunction prior to treatment. Second, the prospective design also allowed us to assess patient-rated symptoms in a longitudinal rather than a cross-sectional design^{2,13,14,19,21,30-32} which is a prerequisite to assess possible dose-volume effect relationships in potential swallowing organs at risk (SWOARs).

One of the shortcomings of studies reporting on the relationship between dose-volume parameters and RISD is that only univariate relationships were estimated^{2,13,17,18,30–34}. In the present study, we used a multivariate logistic regression analysis with bootstrapping as described by El Naqa et al.²⁹. As pointed out by these authors, prediction of endpoints like SWALM6 can be improved by mixing clinical and dose-volume factors, while bootstrap-based variable selection analysis increases the reliability of the predictive models. Indeed, our results showed higher performance of the multivariate model compared to the univariate relationships between dose-volume parameters and SWALM6. Moreover, the multivariate approach and the nomograms allow for an integration of different prognostic variables in estimating the risk on SWALM6 in individual patients. In this regard, it should be stressed that dose-effect relationships for this endpoint should be described by multiple NTCP curves rather than by one single NTCP curve.

In a previous study, we reported on a predictive model on SWALM6 in which dose-volume parameters were not taken into account²⁰. In that study, T3-T4 stage, bilateral neck irradiation, weight loss prior to radiotherapy, primary tumor site in the oropharynx or nasopharynx, concurrent chemoradiation and accelerated radiotherapy were identified as risk factors for the same endpoint as used in the current analysis. The majority of these prognostic factors, such as T-stage (larger volumes), bilateral neck irradiation and primary tumor site significantly correlate with the mean dose in the PCM superior and supraglottic larynx. The fact that the addition of concurrent chemotherapy to radiation and accelerated radiotherapy were not selected by the multivariate analysis as prognostic factors in the current study, suggests that the higher incidence of SWALM6 with these treatment regimens are mainly explained by larger tumor volumes with subsequent larger irradiated volumes of the SWOARs, rather than the treatment regimens itself.

The present study shows a difference in the predictive models found for the different patient-rated swallowing problems regarding food consistencies. Moreover, the results suggest a relationship between food consistency and the anatomical localisation related to that specific problem. At first sight, this may seem rather confusing. However, these different results can be well explained when taking into account the normal swallowing process, which involves multiple muscles and structures. When viscosity increases the pressure generated by the swallow mechanism needs to be increased as well³⁵. This pressure is built up from cranial to caudal, meaning the higher the food viscosity, the more cranial the pressure build-up needs to be initiated. This may very well explain the superior PCM to be most important for solid food. Laryngeal elevation and cricopharyngeal opening is necessary for pharyngeal clearance. Lack of pharyngeal clearance may lead to patient's self-restriction in the amount and viscosity of food taken^{36,37}. In combination with inadequate airway closure at the supraglottic larynx, this could lead to aspiration³⁸. These findings are in agreement with the findings of the present study, in which the SWOARs identified for aspiration were the supraglottic larynx and EIM.

An important finding of the present study is the selection of the radiation technique IMRT as a positive prognostic factor for patient-rated problems with swallowing liquids

and soft food. In an earlier study, Vergeer et al.⁸ found lower scores for patient-rated swallowing dysfunction as assessed by the EORTC QLQ-H&N35, when treated with IMRT compared with standard 3D-CRT, probably due to lower doses in the normal tissues. One might expect that the mean dose in the SWOARs is lower with IMRT compared to 3D-CRT, however this was not the case in our cohort (data not shown). In fact, the mean total doses to all SWOARs did not differ between the 3D-CRT and IMRT patients (data not shown). However, it should be taken into account that with the IMRT SIB technique, the prescribed fraction dose to the elective regions was 1.55 Gy given in 35 fractions in 6-7 weeks as compared to 2 Gy per fraction up to a total dose of 46 Gy in 4-5 weeks when 3D-CRT was used. From a radiobiological point of view, the lower dose per fraction and possibly the prolongation of the overall treatment time of the elective dose may very well explain the lower incidence of patient-rated swallowing dysfunction 6 months after completion of (CH) RT. Moreover, these results are in line with those reported by Bhide et al.³⁹ in relation to acute toxicity.

A number of other authors reported on the relationship between patient-rated swallowing dysfunction after (CH) RT and dose distributions in SWOARs^{2,19,21,31,33,34}. In summary, the dose distributions in different parts of the PCM, dose to the (supraglottic) larynx, the pre-treatment swallowing problems and use of brachytherapy were found to be associated with different kinds of patient-rated swallowing dysfunction, which is in line with the findings of the present study.

Conclusion

We developed predictive models for physician-rated and patient-rated swallowing dysfunction in HNC patients treated with (CH) RT, using multivariate bootstrap logistic regression analysis. The results of our study illustrate that these different endpoints cannot be predicted with univariate relationships between dose distribution in a single SWOAR and these endpoints, but that separate NTCP models are needed for different endpoints, and that factors other than DVH parameters are important as well. These results are currently being validated in a subsequent cohort study at our institutions.

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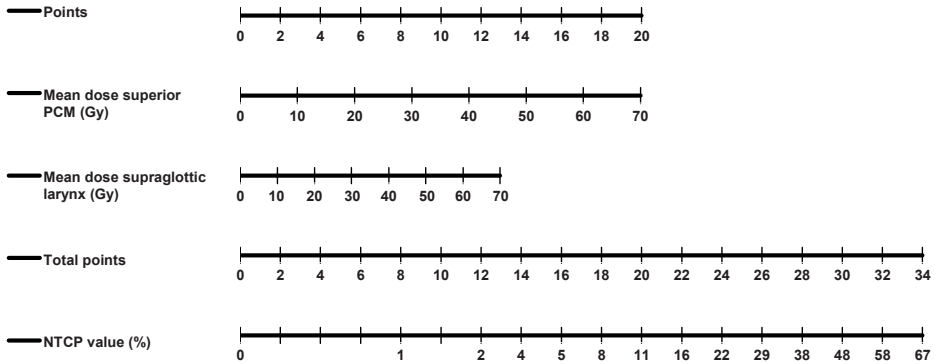
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Appendices

Appendix A: Nomogram for SWALM6 to determine NTCP values for each individual patient

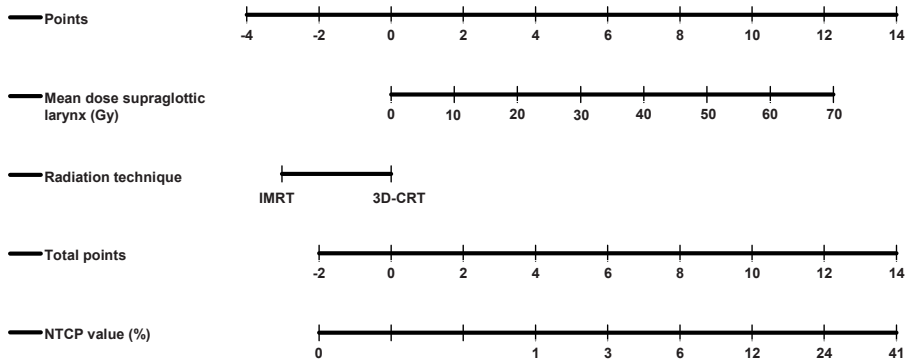
Nomogram: Grade 2-4 swallowing dysfunction



Abbreviations: NTCP=normal tissue complication probability, PCM=pharyngeal constrictor muscle.

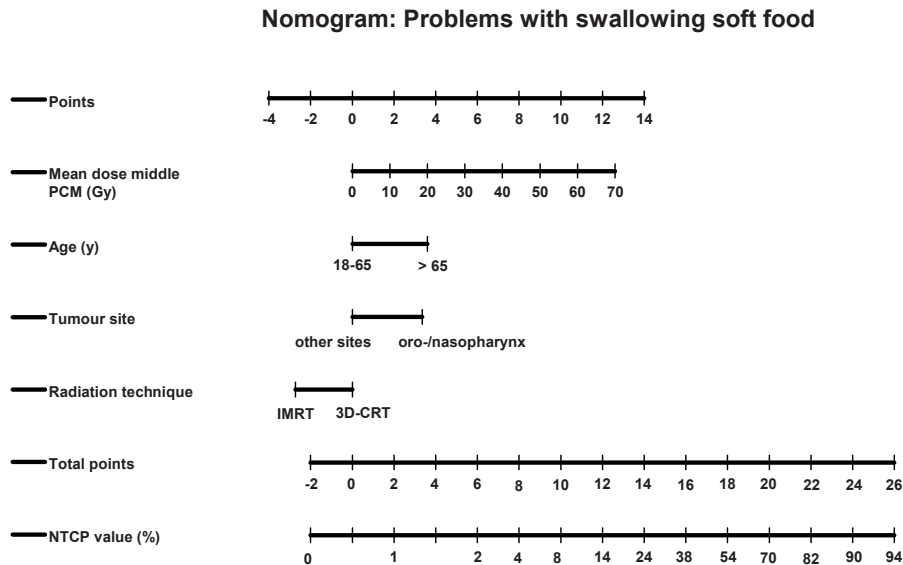
Appendix B1: Nomogram for problems with swallowing liquids to determine NTCP values for each individual patient

Nomogram: Problems with swallowing liquids



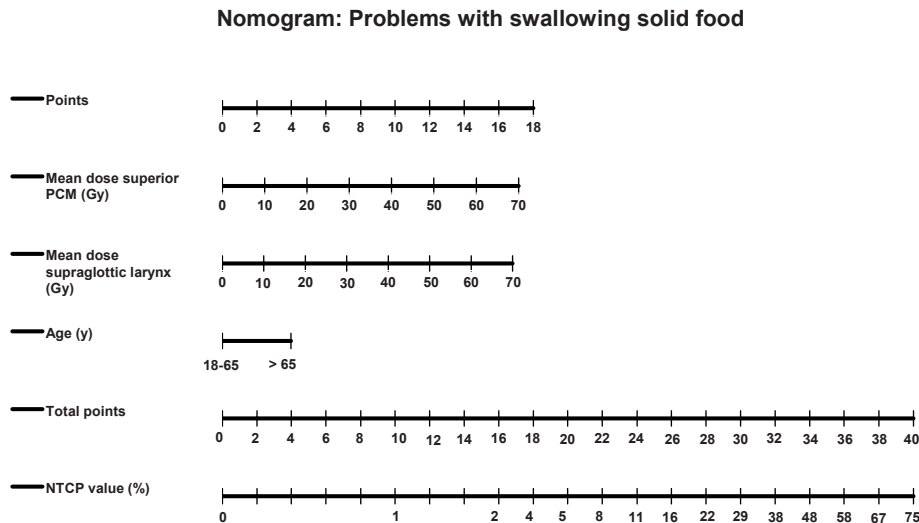
Abbreviations: 3D-CRT=3D conformal radiotherapy, IMRT=intensity modulated radiotherapy, NTCP=normal tissue complication probability.

Appendix B2: Nomogram for problems with swallowing soft food to determine NTCP values for each individual patient



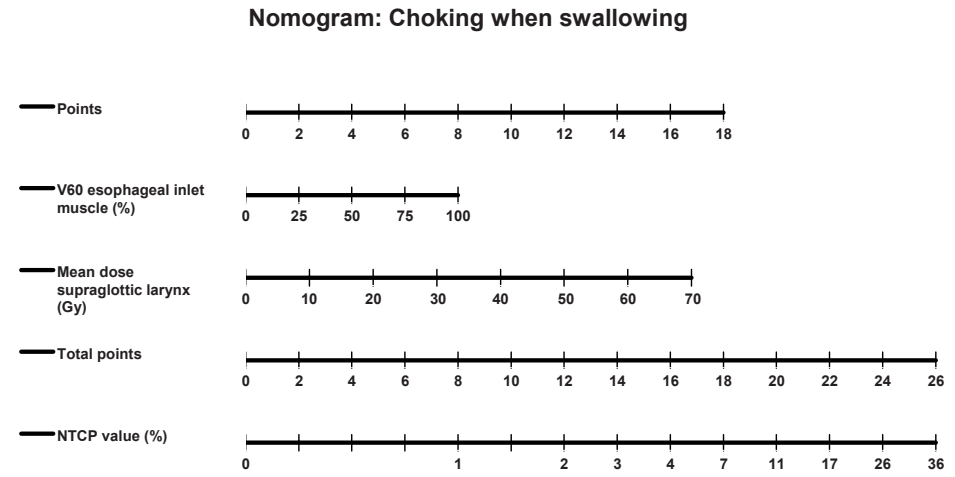
Abbreviations: 3D-CRT=3D conformal radiotherapy, IMRT=intensity modulated radiotherapy, NTCP=normal tissue complication probability, PCM=pharyngeal constrictor muscle.

Appendix B3: Nomogram for problems with swallowing solid food to determine NTCP values for each individual patient



Abbreviations: NTCP=normal tissue complication probability, PCM=pharyngeal constrictor muscle.

Appendix B4: Nomogram for problems with choking when swallowing to determine NTCP values for each individual patient



Abbreviations: NTCP=normal tissue complication probability, V60=volume receiving ≥ 60 Gy.

